·综述·

铁死亡在神经退行性疾病发病机理中的研究进展

罗　瑶，蒋　梅
(广东医科大学基础医学院，广东 东莞 523808)

摘　要：受人口老龄化趋势影响，阿尔茨海默病(AD)、帕金森病(PD)、亨廷顿病(HD)及肌萎缩侧索硬化症(ALS)等神经退行性疾病发病人数持续上升。这些疾病发病机制复杂，目前临床仍缺少针对性治疗手段。铁死亡作为一种由铁依赖性脂质过氧化驱动的新型程序性细胞死亡方式，广泛参与上述疾病的发生与演变。在病理状态下，铁代谢紊乱与活性氧(ROS)累积均可诱发铁死亡，其中铁过载可通过芬顿反应加剧氧化损伤，破坏谷胱甘肽(GSH)抗氧化防御系统，导致多不饱和脂肪酸(PUFAs)发生严重过氧化，最终造成神经元损伤。此外，铁死亡还与氧化应激、神经炎症、异常蛋白聚集及凋亡等病理过程相互作用，加速病情进展。综合现有研究来看，铁稳态失衡、脂质过氧化增强、GSH 耗竭及谷胱甘肽过氧化酶 4(GPX4)防御受损是上述神经退行性疾病中铁死亡发生的共同基础；同时，铁死亡在上述疾病中也会结合各自的致病蛋白和调控通路，表现出一定的疾病特异性。基于此，本文整理了铁死亡的分子调控机制，梳理了其在 AD、PD、HD 及 ALS 中的研究进展，并总结了不同疾病间的共性机制及差异化调控通路，旨在为疾病机制探究与新药研发提供参考。

关键词：铁死亡；神经退行性疾病；程序性细胞死亡；铁代谢紊乱；氧化应激
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Research Progress on Ferroptosis in the Pathogenesis of Neurodegenerative Diseases

LUO Yao, JIANG Mei
(School of Basic Medical Sciences, Guangdong Medical University, Dongguan 523808, China)
Correspondence to: JIANG Mei; E-mail: Jiangm528@gdmu.edu.cn

Abstract: Driven by the global trend of population aging, the prevalence of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS), has been rising consistently. The pathogenic mechanisms of these disorders are complex, and effective disease-modifying therapies remain an unmet clinical need. Ferroptosis, a regulated cell death modality driven by iron-dependent lipid peroxidation, has been widely implicated in the occurrence and evolution of the aforementioned conditions. Under pathological states, both perturbed iron metabolism and reactive oxygen species (ROS) accumulation can precipitate ferroptosis. Specifically, iron overload exacerbates oxidative injury via the Fenton reaction, disrupts the glutathione (GSH)-based antioxidant defense system, and induces extensive peroxidation of polyunsaturated fatty acids (PUFAs), ultimately culminating in neuronal damage. Furthermore, ferroptosis interacts synergistically with other pathological hallmarks, such as oxidative stress, neuroinflammation, aberrant protein aggregation, and apoptosis, thereby accelerating disease progression. A synthesis of current evidence indicates that disrupted iron homeostasis, enhanced lipid peroxidation, GSH depletion, and impaired glutathione peroxidase 4 (GPX4) activity constitute the common basis for

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作者简介：罗瑶，第一作者，研究方向：神经退行性疾病，E-mail：13826823158@163.com；蒋梅，通信作者，副教授，研究方向：神经退行性疾病，E-mail：Jiangm528@gdmu.edu.cn

ferroptosis in these neurodegenerative diseases. Concurrently, ferroptosis also displays certain disease-specific characteristics by engaging distinct pathogenic proteins and regulatory pathways in each disorder. In this review, we delineate the molecular regulatory framework of ferroptosis, summarize its research progress in AD, PD, HD, and ALS, and highlight both shared mechanisms and divergent regulatory pathways across these diseases, with the goal of informing future investigations into disease pathogenesis and the discovery of novel strategies.

Key words: ferroptosis; neurodegenerative disease; programmed cell death; iron metabolism disorder; oxidative stress

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当下,铁死亡在阿尔茨海默病(Alzheimer's disease, AD)、帕金森病(Parkinson's disease, PD)、亨廷顿病(Huntington's disease, HD)及肌萎缩侧索硬化症(amyotrophic lateral sclerosis, ALS)等神经退行性疾病中的作用,已经成为领域内的研究重点。现有相关综述大多单独探讨某一种疾病[1-2],或是聚焦特定信号通路[3],尚未系统归纳不同神经退行性疾病中铁死亡存在的共性规律与特异性调控机制。上述疾病的病因及临床表现虽存在差异,但铁代谢紊乱、氧化应激、脂质过氧化、神经炎症及异常蛋白沉积是其共有的病理特征,且这些过程与铁死亡密切相关[4],共同参与神经元损伤[5]。鉴于此,本文从铁死亡相关的各类病理过程入手,梳理其分子调控机制,并结合AD、PD、HD及ALS等代表性神经退行性疾病的发病机理,系统比较铁死亡在不同疾病中的共同分子机制与差异通路,以期从多角度阐释铁死亡介导神经退行性病变的内在机制,为治疗方案优化和药物研发提供理论基础。

1 铁死亡

铁死亡是Stockwell团队[6]于2012年筛选抗肿瘤药物Erastin时首次定义命名的新型程序性细胞死亡方式。不同于凋亡、坏死、自噬,铁死亡无细胞膜起泡或染色体凝集现象,特征为线粒体变小、膜密度增加及线粒体嵴减少,依靠铁依赖性脂质过氧化物过度积累启动死亡过程,以细胞内铁稳态失衡与氧化应激增强为主要特征。铁死亡广泛参与了多种疾病及生理病理过程,包括肿瘤与免疫应答、急性肾损伤、缺血再灌注损伤以及败血症等[7]。近年来,铁死亡的调控机制逐渐被证实与神经系统疾病密切相关。一方面,中枢神经系统具有较高的氧消耗率,且富含易发生脂质过氧化的多不饱和脂肪酸(polyunsaturated fatty acids, PUFAs);另一方面,脑内铁会随年龄增长发生慢性异常沉积,长期持续的铁过载联合谷胱甘肽(glutathione, GSH)稳态耗竭,会重塑神经元氧化防御系统,使神经元进入慢性铁死亡应激状态,进而对铁依赖的脂质过氧化损伤极其敏感[8]。在AD、PD、HD、ALS等神经退行性疾病中,均伴随脑内异常铁沉积与氧化应激升高,造成神经元不可逆损伤。已有研究证实,铁死亡是上述疾病中神经元丢失的重要诱因,干预铁代谢、抑制脂质过氧化可显著减轻神经损伤并延缓疾病进程[9]。因此,探究铁死亡在神经退行性疾病中的调控机制,有助于发掘新的治疗靶点,为临床药物研发与疾病治疗提供新思路。

1.1 氧化应激

在神经退行性疾病中,铁死亡与氧化应激之间有密切的相互作用。过量活性氧(reactive oxygen species, ROS)可损伤线粒体功能,导致能量代谢障碍、钙稳态失调及神经元死亡,进而破坏脑内神经传递与氧化还原平衡。铁离子(尤其是Fe^{2+})在氧化应激引起的细胞死亡中起着重要作用。Fe^{2+}可与H_2O_2通过芬顿反应直接产生羟基自由基,从而启动非酶促脂质过氧化;在Fe^{2+}存在的情况下,脂质过氧化氢可转化为烷氧基自由基,与邻近的PUFAs发生反应,启动新一轮脂质自由基链式扩增(图1)[10]。这种由铁介导的脂质过氧化正反馈放大过程,一旦超出细胞自身调控能力,就会导致细胞膜结构破坏,最终引发细胞死亡,特别是铁死亡。近年来的研究发现,在AD和PD等常见神经退行性疾病中,氧化应激失衡与ROS大量蓄积所诱发的线粒体损伤通路,是扰乱中枢神经信号传递、破坏脑内氧化还原平衡的关键病理环节[11]。

1.2　脂质过氧化

磷脂、胆固醇与鞘脂是构成细胞膜的主要成分，对维持细胞的结构完整性至关重要。氧化应激过程中产生的ROS会引发脂质过氧化反应，导致脂质分子的碳链被氧化、断裂和缩短，进而损害细胞膜的结构与功能[12]。铁依赖性磷脂过氧化是触发铁死亡的核心因素，在药理干预研究中，促铁死亡的小分子工具药根据作用靶点主要分为2类：一类为System Xc^-抑制剂，包括Erastin、柳氮磺胺吡啶，主要通过抑制细胞System Xc^-转运体功能，造成胞内GSH合成障碍、抗氧化系统失活，间接诱发脂质过氧化物累积；另一类为谷胱甘肽过氧化酶4（glutathione peroxidase 4，GPX4）直接抑制剂，以RAS-选择性致死分子3（RAS-selective lethal 3，RSL3）为代表，可直接靶向抑制铁死亡核心调控蛋白GPX4的活性，打破细胞脂质抗氧化平衡，快速诱导铁死亡发生。同时，铁死亡还可被亲脂抗氧化剂（如辅酶Q10、维生素E、铁抑素-1、脂抑素-1）所抑制[13-15]。细胞内铁浓度升高、抗氧化物质GSH耗竭，会显著增加脂质过氧化程度和ROS累积，最终驱动铁死亡发生[16]。PUFAs是神经元膜磷脂的重要组成部分，富含多个不饱和双键，易被氧化，是脂质过氧化反应的主要靶点，并直接参与铁死亡过程。研究表明，酰基辅酶A合成酶长链家族成员4（acyl-CoA synthetase long-chain family member 4，ACSL4）可催化游离PUFAs，并在溶血磷脂酰胆碱酰基转移酶3（lysophosphatidylcholine acyltransferase 3，LPCAT3）作用下酯化生成含多不饱和酰基尾的磷脂，后者可经脂氧合酶催化或自氧化生成脂质过氧化物，从而诱发铁死亡（图1）[17-19]。除经典的GPX4途径外，细胞内还存在补充性的内源性脂质过氧化防御机制。Bersuker等研究者发现，铁死亡抑制蛋白1（ferroptosis suppressor protein 1，FSP1）可通过N端豆蔻酰化修饰定位至细胞膜，催化氧化型辅酶Q10转化为还原态辅酶Q10，从而抑制脂质过氧化和铁死亡发生。这一发现补充了脂质过氧化的内源性调控网络，也为铁死亡相关疾病的靶向药物研发提供了重要策略[20]。

1.3　炎症反应

神经炎症与铁死亡相互作用，共同构成了神经退行性病变的病理网络。在病理微环境中，脂多糖（lipopolysaccharide，LPS）刺激可上调ACSL4的表达，既改变脂质代谢诱导小胶质细胞发生铁死亡，又激活核因子-κB（nuclear factor kappa B，NF-κB）通路，促使M1型小胶质细胞大量分泌肿瘤坏死因子-α（tumor necrosis factor-alpha，TNF-α）、白细胞介素（interleukin，IL）-1β、IL-6、IL-8与过量一氧化氮（nitric oxide，NO）[21-22]。这些促炎介质会扰乱神经元铁代谢并提升其脂质过氧化水平；而神经元发生铁过载后，又会反馈性上调二价金属转运蛋白1（divalent metal transporter 1，DMT1）与铁蛋白的表达，同时借助铁调素抑制铁转运蛋白1（ferroportin 1，FPN1）的功能，从而进一步加剧胞内铁蓄积（图1）。最终，发生铁死亡的神经元会向胞外释放损伤相关分子模式（damage-associated molecular patterns，DAMPs），持续激活小胶质细胞，形成“炎症-铁死亡”循环。这种恶性循环还与小胶质细胞的表型异质性密切相关：抗炎的M2型小胶质细胞对铁死亡较为敏感，抑制铁死亡有助于发挥其保护作用；而促炎的M1型小胶质细胞则具有铁死亡抗性，可在铁过载微环境中持续分泌炎性介质，加剧病程进展[23-24]。

1.4　凋　亡

尽管铁死亡和凋亡在形态结构及生化机制上具有显著区别，但两类程序性细胞死亡之间可发生信号交叉，能够彼此调控。目前已有PD相关研究表明，铁死亡和凋亡可协同作用，推动神经元损伤进程。α-突触核蛋白发生病理性聚集之后能够造成线粒体受损、ROS堆积；不断累积的脂质过氧化产物损伤线粒体膜，进而诱发凋亡。而凋亡诱发的线粒体稳态失衡、抗氧化能力下降，又会反向加剧铁死亡，加速神经元受损[25]。在肿瘤、肾脏等非神经系统模型中，2种死亡方式的交互调控机制已得到较多证实。肿瘤相关研究表明，Bcl-2家族蛋白、内质网应激、p53等关键分子可介导两条通路交叉联动，外界应激条件下细胞可出现铁死亡与凋亡表型相互转化的现象[26-28]。肾脏损伤模型同样证实二者存在上下游调控关系，尿毒症毒素可诱导肾小管细胞发生铁死亡，并进一步激活Bax、细胞色素C介导的凋亡通路；且抑制铁死亡可有效缓解后续凋亡损伤，而阻断凋亡无法逆转铁死亡所致的细胞损伤，说明铁死亡可正向驱动凋亡发生[29]。整体而言，目前铁死亡与凋亡交叉的研究主要集中在肿瘤和肾脏领域，神经系统中的研究尚待深入，因此非

神经系统得出的调控规律,可以为本领域后续机制探究提供参考。

1.5 蛋白质聚集

蛋白质异常聚集是神经退行性疾病的共同病理特征,且能直接诱导或调控铁死亡。在AD和PD中,β-淀粉样蛋白(β-amyloid, Aβ)与α-突触核蛋白寡聚体可破坏细胞膜及线粒体功能,导致ROS水平剧烈升高与脂质过氧化[30-31]。在HD中,突变型亨廷顿蛋白(mutant huntingtin, mHTT)异常聚集可通过Nrf2/ARE通路影响GSH合成、还原型烟酰胺腺嘌呤二核苷酸磷酸再生(维系GPX4活性)、铁/脂质代谢及线粒体动态,调控铁死亡转归[32]。在ALS的病理生理中,超氧化物歧化酶1(superoxide dismutase 1, SOD1)的异常聚集主要通过靶向抑制GPX4轴,直接诱导脂质过氧化并激活铁死亡[33];TDP-43的异常聚集通常伴随着核内TDP-43的功能丧失,而TDP-43突变或功能丧失会导致关键合成酶GCLM下调,引发GSH严重耗竭与ROS累积;这切断了GPX4的抗氧化底物来源并促使脂质过氧化与TDP-43进一步异常聚集,形成诱发神经元死亡的恶性循环[34]。从分子级联来看,异常铁及错误配位铁在诱导蛋白质聚集的同时,会诱导细胞内ROS的大量生成。这些过量的ROS进一步引发脂质过氧化,并与蓄积的铁协同作用,最终导致细胞发生铁死亡[35]。铁死亡与蛋白病理聚集构成了双向正反馈回路:异常聚集蛋白可诱发铁死亡,而铁死亡引发的脂质过氧化、糖原合成酶激酶-3β(glycogen synthase kinase-3β, GSK-3β)激活以及蛋白酶体功能障碍,亦会反向加速Tau蛋白的磷酸化与沉积[36]。因此,蛋白质聚集与铁死亡相互促进,共同驱动了神经元的持续退变(图1)。

2 铁死亡在不同神经退行性疾病中的研究进展

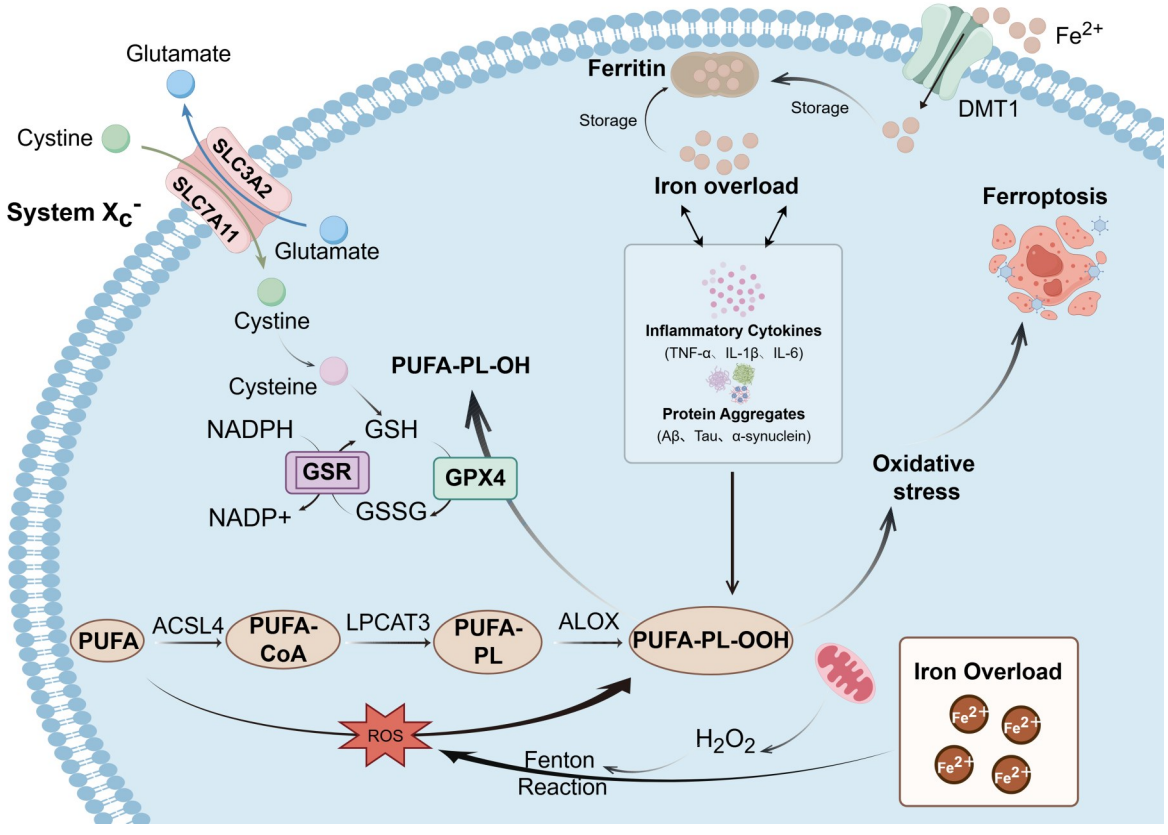
AD、PD、HD以及ALS等常见神经退行性疾病,均以中枢系统内的突触减少、神经元慢性进行性变性为主要特征。现有文献表明,铁死亡作为铁依赖性细胞死亡的新机制,在这些疾病的发生演变中扮演着关键角色。

2.1 阿尔茨海默病

AD作为临床常见的神经退行性病变,其发病机制在根源上依赖于两点,即细胞外Aβ聚集导致的老年斑块,以及细胞内部过度磷酸化的tau蛋白缠结。这些异常病变交织,进而造成突触流失并引发神经元功能障碍[37]。AD患者脑内铁沉积主要发生于深部灰质、颞下皮层,与患者记忆丧失、认知能力下降密切相关;有研究利用定量磁化率成像(quantitative susceptibility mapping, QSM)发现AD患者颞叶和额叶的磁化率升高,且这种升高与认知功能下降显著相关[38]。研究发现,AD患者大脑内的Aβ沉积会造成铁蓄积,进而触发铁死亡,表明铁死亡是AD进展过程中的关键病理环节(表1)[39-41]。大量临床前动物实验显示,铁螯合剂可有效调控AD模型小鼠的脑铁稳态。其中地拉罗司能够减轻由铁过载所诱导的Tau/APP转基因小鼠脑内tau蛋白过度磷酸化水平[42];M30则可降低APP/PS1小鼠大脑中的Aβ沉积与铁含量,并显著改善其认知功能缺损[43];辅酶Q10本身具备抗炎与抗氧化活性,有研究利用脂肪干细胞外泌体对其进行递送,结果显示模型动物的认知、记忆功能及神经增殖状态均得到改善[44],证实它可对Aβ诱导的神经损伤起到保护作用。以上成果,也为靶向铁死亡研发AD治疗药物提供了新方向(图2)。

2.2 帕金森病

PD是第二大高发神经退行性疾病,该病典型病理改变为黑质致密部多巴胺能神经元的进行性丢失,以及α-突触核蛋白异常聚集形成的细胞内路易小体沉积[45],最终严重损伤中枢神经系统的运动功能,患者多表现为静止性震颤、肌肉僵硬、运动迟缓与平衡障碍等症状。临床样本与动物模型均证实,PD患者黑质致密部存在明显铁蓄积,且这一现象和病情发展高度关联(表1)[46]。现有研究证明,铁沉积诱发的铁死亡,是造成多巴胺能神经元丢失的关键原因,也为PD治疗提供了新靶点[47]。Sheng等[48]研究发现,分别在MPP^+和MPTP诱导的PD细胞和小鼠模型中,TP53诱导的糖酵解和凋亡调节因子(TP53-induced glycolysis and apoptosis regulator, TIGAR)表达显著下调,并伴随铁离子蓄积、脂质过氧化增强及多巴胺能神经元损伤;而过表达TIGAR后,神经元铁死亡得到抑制,铁沉积减少,多巴胺能神经元也得到有效保护,说明TIGAR



System Xc^-: cystine/glutamate antiporter ; SLC7A11: solute carrier family 7 member 11; SLC3A2: solute carrier family 3 member 2; GSSG: oxidized-glutathione; GSR: glutathione reductase; NADPH: nicotinamide adenine dinucleotide phosphate-reduced; $NADP^+$: nicotinamide adenine dinucleotide phosphate-oxidized; GSH: glutathione; GPX4: glutathione peroxidase 4; PUFA: polyunsaturated fatty acid; PUFA-CoA: polyunsaturated fatty acid-coenzyme A; PUFA-PL: polyunsaturated fatty acid-containing phospholipids; ALOX: arachidonate lipoxygenase; PUFA-PL-OOH: polyunsaturated fatty acid hydroperoxides (Lipid Hydroperoxide); ACSL4: acyl-CoA synthetase long-chain family member 4; LPCAT3: lysophosphatidylcholine acyltransferase 3; H_2O_2: hydrogen peroxide; DMT1: divalent metal-ion transporter 1; ROS: reactive oxygen species; Aβ: amyloid-beta; Tau: tau protein; α-synuclein: alpha-synuclein; PUFA-PL-OH: polyunsaturated fatty acid alcohols (Non-toxic lipid alcohols); IL-1β: interleukin-1 beta; IL-6: interleukin-6; TNF-α: tumor necrosis factor alpha. This figure was drawn by Figdraw.

图1　铁死亡的主要途径和分子机制

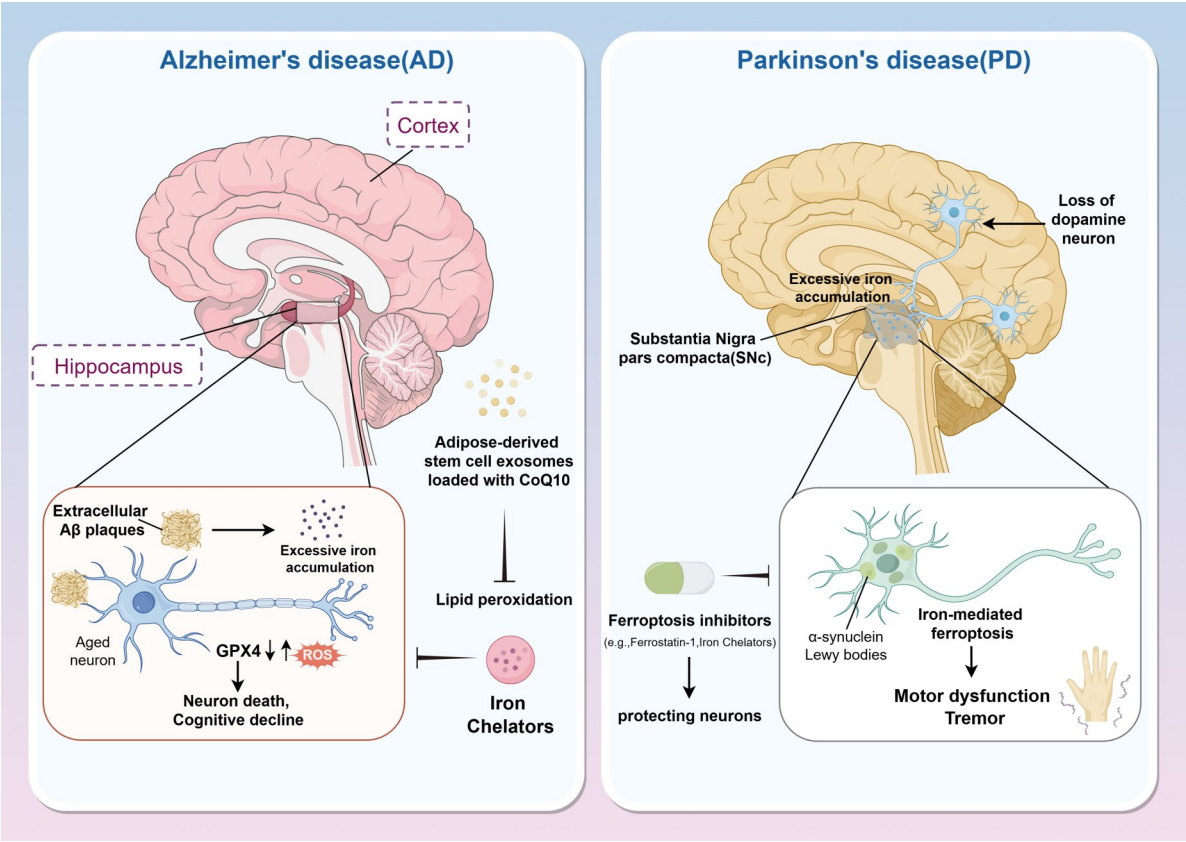
Fig. 1　Key pathways and molecular mechanisms of ferroptosis

能通过调控氧化还原稳态参与PD相关铁死亡过程。目前，去铁酮、去铁胺等铁螯合剂，以及辅酶Q10、N-乙酰半胱氨酸等抗氧化剂，均可靶向铁死亡改善PD相关症状，具备良好研发前景。不过这类药物的临床试验尚处于早期阶段，仍需更多研究验证实际疗效(图2)[47, 49-50]。

2.3　亨廷顿病与肌萎缩侧索硬化症

除了AD和PD，铁死亡在其他神经退行性疾病的病理进展中也起着关键作用，其机制和治疗潜力已得到广泛研究，其中对HD、ALS的研究相对充分。

HD是*HTT*基因CAG三核苷酸重复扩增导致的单基因遗传性神经退行性疾病[51]，其特征是纹状体和大脑皮层投射神经元的进行性丢失，并伴有星形胶质细胞异常及脑组织萎缩[52]。临床与动物模型研究显示，HD患者血浆脂质中存在高水平脂质过氧化产物，同时GSH水平显著降低；这种氧化还原失衡现象在HD动物模型的脑组织中同样存在，且氧化应激发生于HD临床症状出现之前，这表明它是疾病进展的一个早期因素[53-55]。脂质过氧化产物过度蓄积、GSH耗竭正是铁死亡发生的核心前提，结合HD患者与模型动物脑组织中均存在神经元铁异常蓄积的现象，可证实铁死亡是HD中神经元进行性丢失的重要细胞死亡方式，铁代谢异常与疾病进展密切相关(表1)[56-57]。此外，HD中星形胶质细胞的铁死亡也参与了神经退行性进程，星形胶



Aβ: amyloid-beta; GPX4: glutathione peroxidase 4; ROS: reactive oxygen species; CoQ10: coenzyme Q10. This figure was drawn by Figdraw.

图2 铁死亡在AD与PD中的致病机制及干预示意图

Fig. 2 Schematic diagram of the pathogenic mechanisms and interventions of ferroptosis in AD and PD

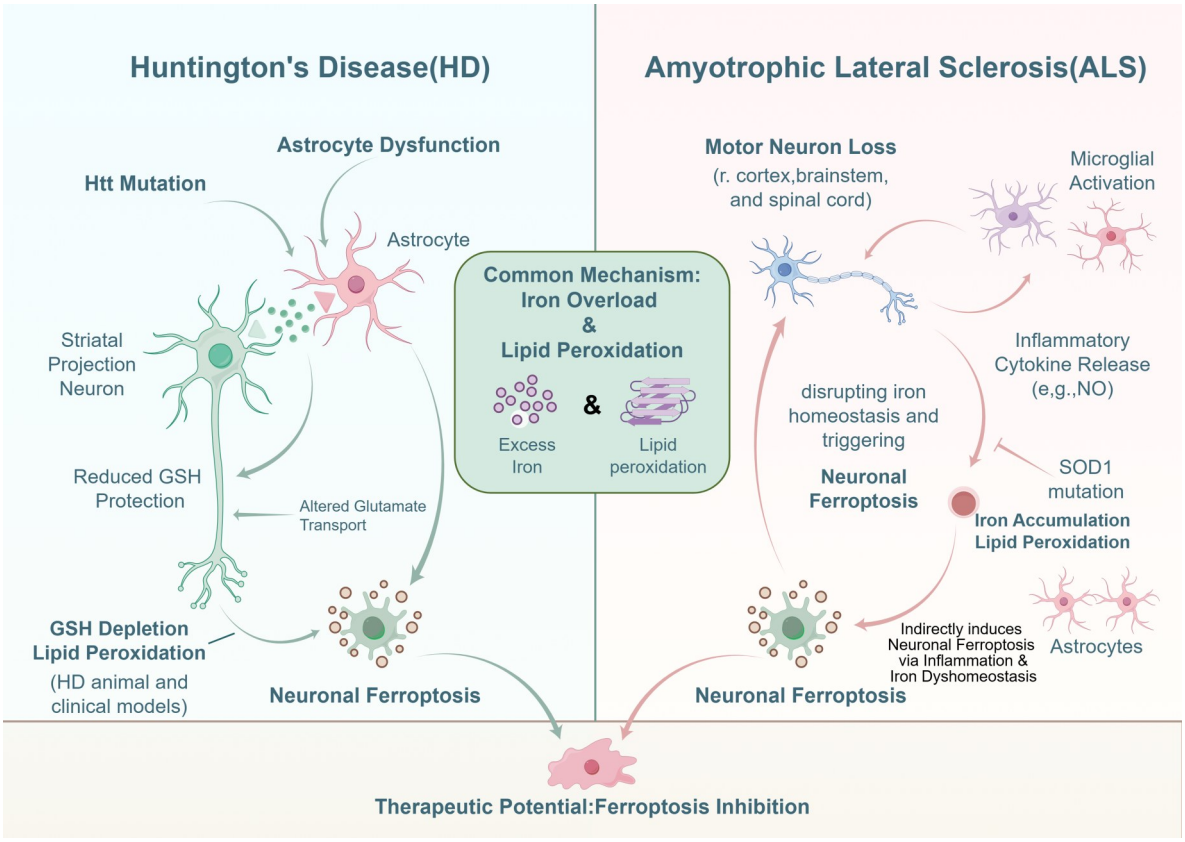
质细胞中mHTT的表达可引发基因表达谱异常,导致谷氨酸转运体功能受损、细胞外谷氨酸水平异常升高,从而加重神经元氧化应激与铁过载;而星形胶质细胞铁死亡会进一步破坏其对神经元的代谢支持与抗氧化保护作用,间接诱导神经元死亡,加剧HD的病理进展[58-59]。现有研究表明,调节铁代谢、抑制铁死亡可减轻HD相关病理损伤,延缓疾病病程,为HD治疗提供了新的潜在方向(图3)[60-61]。

ALS是一种致死性神经退行性运动神经元疾病,其最主要的病理特征为大脑皮层、脑干与脊髓中的运动神经元进行性变性丢失,具体表现为大脑皮层Brodmann 4区Ⅴ层Betz细胞(上运动神经元)、脑干运动核与脊髓前角雷克斯德Ⅸ层α运动神经元(下运动神经元)的选择性死亡[62]。临床与动物模型研究已经证实,ALS患者脑组织与脊髓中存在异常的铁代谢和铁聚集[63]。胶质细胞,尤其是小胶质细胞,在ALS中不仅呈铁染色阳性,还通过"非细胞自主性"机制加剧神经元损伤。研究发现,亚致死性铁死亡应激可激活小胶质细胞,促使其分泌大量NO等炎症因子,进一步扰乱神经元铁稳态、诱发铁过载与脂质ROS积累,形成"胶质-神经元"恶性循环(表1)[64]。在ALS模型中过表达GPX4可显著降低SOD1突变体的细胞毒性,延缓ALS发病,改善运动神经元功能,并延长模型动物生存期[65-66]。上述证据证实,铁死亡是ALS中运动神经元丢失的重要驱动机制,抑制运动神经元铁死亡具有治疗ALS的潜在希望(图3)。

2.4 铁死亡在不同神经退行性疾病中的共性机制与差异通路

AD、PD、HD与ALS虽受累神经元及临床表型各异,但其铁死亡过程既存在共同的分子机制,又因遗传背景与病理微环境的差异呈现出特异的调控网络。

从共性机制来看,上述疾病中铁死亡的启动均遵循"铁稳态失衡-脂质过氧化-抗氧化防御崩溃"这一核心轴。局部的铁沉积是触发铁死亡的物理基础;无论是AD的海马、PD的黑质致密部、HD的



GSH: glutathione; NO: nitric oxide; SOD1: superoxide dismutase 1. This figure was drawn by Figdraw.

图3　铁死亡在HD与ALS中的致病机制及干预示意图

Fig. 3　Schematic Diagram of the Pathogenic Mechanisms and Interventions of Ferroptosis in HD and ALS

表1　铁死亡在主要神经退行性疾病中的病理特征及干预策略

Table 1　Pathological features and intervention strategies of ferroptosis in major neurodegenerative diseases

Disease	Core pathological features	Ferroptosis-related pathology	Potential intervention strategies / inhibitors	References
AD	Aβ deposition, hyperphosphorylated tau protein	Iron deposition in hippocampus and cortex; Aβ-induced iron accumulation	Iron chelators, Coenzyme Q10	[40, 44]
PD	Loss of dopaminergic neurons, α-synuclein aggregation	Abnormal iron deposition in the substantia nigra pars compacta	Iron chelators, Antioxidants	[49-50]
HD	*HTT* gene mutation, loss of striatal neurons	Decreased GSH levels, elevated lipid peroxidation products, neuronal iron accumulation	Antioxidants, Regulation of iron metabolism	[60-61]
ALS	Progressive degeneration and loss of motor neurons	Abnormal iron accumulation in ventral spinal motor neurons and glial cells	Enhancing GPX4 activity, inhibiting motor neuron ferroptosis	[64, 66]

AD: Alzheimer's disease; tau: tau protein; Aβ: amyloid-beta; PD: Parkinson's disease; α-synuclein: alpha-synuclein; HD: Huntington's disease; HTT: huntingtin; GSH: glutathione; ALS: amyotrophic lateral sclerosis; GPX4: glutathione peroxidase 4.

纹状体还是ALS的脊髓前角，蓄积的Fe^{2+}均能通过芬顿反应生成高活性羟基自由基，引发PUFAs的脂质过氧化，破坏细胞膜完整性。同时，GSH耗竭与GPX4功能失活是各类神经元走向铁死亡的共同终

末事件。此外,胶质细胞发生铁死亡应激后释放的促炎因子与NO,也在不同疾病中普遍构成了"胶质细胞-神经元"互作的毒性放大机制。

从差异通路来看,4种神经退行性疾病诱发铁死亡所涉及的作用分子、受累细胞类型及下游调控信号存在区别。AD病变主要累及海马与皮层神经元,Aβ、过度磷酸化Tau可与铁死亡形成双向恶性循环。近年体内外系列研究证实,成纤维细胞生长因子22(fibroblast growth factor 22, FGF22)/成纤维细胞生长因子受体2(fibroblast growth factor receptor 2, FGFR2)/Yes相关蛋白(Yes-associated protein, YAP)信号轴是AD特征性保护调控通路。在$A\beta_{1-42}$造模体系中,病理多肽能够抑制YAP核转位,下调溶质载体家族7成员11(solute carrier family 7 member 11, SLC7A11)、GPX4抗氧化蛋白表达,加剧胞内游离铁蓄积与脂质过氧化,最终驱动神经元铁死亡发生。外源性给予FGF22可特异性结合膜受体FGFR2,恢复YAP核转运活性,恢复抗氧化蛋白水平,减少丙二醛(malondialdehyde, MDA)与游离铁积累,同时改善突触损伤、缓解模型小鼠认知衰退[67]。PD具有黑质致密部多巴胺能神经元选择性损伤特征,近年研究提出沉默信息调节因子3(sirtuin 3, SIRT3)/乙酰辅酶A合成酶2(acetyl-CoA synthetase 2, ACSS2)/视神经萎缩蛋白1(optic atrophy 1, OPA1)信号轴是该病潜在线粒体保护通路。临床样本与6-羟基多巴胺(6-hydroxydopamine, 6-OHDA)模型均观察到线粒体SIRT3表达、酶活性下降。SIRT3经去乙酰化激活ACSS2,调控乙酰辅酶A核转运,上调OPA1转录,维持线粒体稳态、减少脂质氧化;病理状态下该通路受损,线粒体稳态失衡诱发多巴胺能神经元铁死亡,动物实验提示激活SIRT3或上调OPA1具备潜在保护作用[68]。HD以星形胶质细胞介导的非细胞自主性损伤为特征,近年研究进一步揭示,mHTT可激活两类铁死亡通路,其中经典ACSL4依赖通路不参与体内病程;而5-脂氧合酶(arachidonate 5-lipoxygenase, ALOX5)介导通路为HD特异性核心机制,mHTT通过结合稳定ALOX5辅因5-脂氧合酶激活蛋白(5-lipoxygenase-activating protein, FLAP),放大脂氧合酶催化的脂质过氧化,敲除Alox5可消除纹状体神经元铁死亡、改善小鼠运动缺陷并延长生存期,ALOX5抑制剂齐留通可显著阻断该损伤通路[69]。ALS选择性损伤上下运动神经元,近期研究显示,在*C9orf72*突变相关家族型ALS中,甘氨酸-精氨酸二肽重复蛋白(poly-glycine-arginine, poly-GR)是关键铁死亡驱动因子。相关体外模型数据提示,poly-GR可阻滞Nrf2入核,选择性抑制*SLC7A11*基因转录,削弱细胞胱氨酸转运功能,同时提升胞内游离Fe^{2+}含量,加剧运动神经元脂质过氧化;过表达Nrf2、SLC7A11或使用铁螯合剂去铁酮均可缓解poly-GR诱导的铁死亡损伤,但仍有待体内实验进一步验证[70]。

3 总结与展望

铁死亡作为一种新近被阐明的调节性细胞死亡方式,已被证实广泛参与AD、PD、HD及ALS等神经退行性疾病的发生发展。大量研究表明,铁代谢失衡、脂质过氧化及抗氧化防御系统受损是诱导铁死亡的核心环节,并与氧化应激、神经炎症及异常蛋白聚集等病理过程相互影响,共同促进神经元损伤和疾病进展。近年来,针对铁死亡关键分子及相关信号通路的干预策略不断发展,铁螯合剂、脂质过氧化抑制剂及抗氧化剂等在多种疾病模型中均表现出一定的神经保护作用,为神经退行性疾病的治疗提供了新的研究思路。

然而,目前铁死亡研究向临床转化仍面临诸多挑战。一方面,现有研究证据主要来源于细胞和动物实验,缺乏高质量临床研究验证,基础研究与临床应用之间仍存在较大差距;另一方面,铁死亡尚缺乏特异性生物标志物,不同神经退行性疾病中铁死亡的启动机制及关键调控环节亦存在差异,其与疾病发生发展的因果关系及动态变化规律仍有待进一步阐明。因此,深入解析铁死亡调控网络及其在不同疾病中的作用特点,是推动相关研究向精准干预发展的重要基础。随着单细胞测序、空间组学及多组学分析等新技术的发展,未来有望进一步揭示不同脑区、不同细胞类型中铁死亡的时空动态变化及其调控机制。同时,铁死亡与凋亡、自噬、焦亡等细胞死亡方式之间的相互作用,也有望成为阐释神经退行性疾病共同发病机制的重要突破口,并为靶向铁死亡的精准治疗及临床转化提供新的理论依据。本文以铁死亡相关共同病理过程为主线,系统梳理了其在不同神

经退行性疾病中的作用特点，并对比归纳铁死亡调控通路的共有特征与疾病差异化机制。综合现有研究可以发现，铁稳态失衡、脂质过氧化持续增强及神经炎症激活是多种神经退行性疾病共有的重要病理特征，也是铁死亡介导神经损伤的共同基础。从跨疾病共性病理机制的角度认识铁死亡，有助于进一步理解神经退行性疾病的共同发病规律，并为开发具有广谱干预潜力的新型治疗策略提供新的理论参考。

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（编辑　黄子芸）